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EXAMINER	
GREENE, JAIME M	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,550	WILDENBERG ET AL.	
	Examiner	Art Unit	
	Jaime M. Greene	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-31 and 33* is/are pending in the application.

4a) Of the above claim(s) *30, 31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 9/21/07. Claims 18-31 and 33 are pending. Claims 30, 31 and 33 have been withdrawn and claims 18-29 are under examination on the merits. This action is FINAL.

Withdrawn Objections

2. In light of the amendment to the specification filed 8/14/07, the objection to the specification has been withdrawn.

Withdrawn Rejections

3. In light of the amendment to the claims filed 9/21/07, which includes the cancellation of clams 32 and 34, the 112 2nd paragraph rejections of claims 18-29, 32 and 34 have been withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 18 and 26-27 rejected under 35 U.S.C. 102(b) as being anticipated by Pinkel (Pinkel, et al. US Patent Number 6,562,565, Patented 5/13/03). Claim 18 requires a method of detecting aneuploidy in one or more chromosomes of a subject, comprising 1) producing a fluorescently labeled polynucleotide samples representative of the number of chromosomes in the subject; 2) producing equivalent non-aneuploid fluorescently labeled polynucleotide standards for each chromosome, said label being different from that used to label said sample; 3) mixing said sample and said standard

with a limited amount of binding agent for each chromosome, wherein said binding agents comprise a polynucleotide that is complementary to said sample and said standard for each chromosome immobilized onto microparticles, and said microparticles for each chromosome are distinct on a characteristic selected from the group consisting of size and fluorescent label intensity, wherein the fluorescent label on said microparticles, if present, has a distinct emission spectrum from both the label of said sample and said standard, and wherein the presence of an aneuploidy creates a detectable signal due to non-equal binding of said sample and said standard to said binding agent; and 4) detecting aneuploidy by comparing the signal caused by the unequal binding of said sample and said standard to said binding agent. Dependent claims further require that said sample and said standard are produced from genomic DNA from a somatic cell, a reproductive cell or a gamete (claim 26), that said binding agent comprises a nucleic acid immobilized on a microparticle, and that said nucleic acid having binding specificity for said sample and said standard (claims 27).

Pinkel teaches a method of determining copy number of target nucleic acids using target nucleic acids on a solid surface (binding agent) to which a sample comprising two sets of differentially labeled nucleic acids are hybridized and detecting the copy number (see abstract) (claim 18). Pinkel teaches that the reference probes (i.e. standard) can be genomic DNA isolated from normal cells (i.e. somatic cells) representative of the number of chromosomes in the specimen, and that comparison of the standard to test probe (i.e. sample) permits detection in variations from normal (column 3, lines 16-26) (claims 18, 26). Pinkel teaches that the nucleic acids

(comprising the reference probes and test probes) are labeled with two labels that should be distinguishable (i.e. detection of aneuploidy) (column 2, lines 34-38), and that the labels are usually fluorescent labels (column 3, lines 8-9) (claim 18). Pinkel teaches hybridizing the probes to the target elements (i.e. sample and standard to binding agent) (column 11, lines 28-32), wherein the hybridization involves using immobilized target nucleic acids (column 11, lines 51-53) (claims 18, 27). Pinkel teaches that the target elements (i.e. binding agent) may be on separate supports, such as a plurality of beads (column 2, lines 55-56), and that the target elements are typically from 1μM to 3mM (i.e. microparticles, column 4, lines 26-31) (claim 18). Pinkel also teaches that beads of various sizes can be used (column 8, lines 57-61) (claim 18). Finally, Pinkel teaches detecting the ratio of binding of each probe to each target element, which permits the comparison of copy number (i.e. detection of aneuploidy) (column 2, lines 66-67 and column 3, lines 1-6) (claim 18). Therefore each and every element of these claims is met by the reference.

Response to arguments

Applicant's arguments filed 9/12/07 have been fully considered but they are not persuasive.

Applicant's argue that Pinkel does not teach detecting a signal due to the non-equal binding of sample and standard to the binding agent. However, applicant's attention is drawn to Pinkel, from col 2, lines 66 through col 3, line 27, wherein Pinkel describes that comparing binding of reference probes to target elements with the binding of test probe to target elements can detect variations in copy number from

normal (due to binding differences). Pinkel teaches determining a ration and any ratio that does not equal 1 would indicate nonequal binding. Pinkel also states that the greater the ratio of the binding to the target, the greater the copy number. Therefore, the ratio is a means of detecting the nonequal binding.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., using different amount of test and sample elements) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claim requires producing fluorescently-labeled polynucleotide samples and equivalent fluorescently-labeled polynucleotide standards, however the claim does not indicate the amounts of sample and standard polynucleotide. Therefore, the claim does not require different amounts of sample and standard (described in Applicants' arguments as test and sample elements), and the teachings of Pinkel meet the limitations recited in the claim.

In response to Applicant's arguments that Pinkel teaches away from using size, number or fluorescence, by reciting these options in the alternative, the claim only requires that the method use one of these options. Therefore, since Pinkel teaches using fluorescence, the method of Pinkel teaches the limitation of using fluorescence.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., use of multiple internal controls) are not recited in the rejected claim(s). Although

the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 18 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel as applied to claims 18 and 26-27 above. Claims 18 and 26-27 are described above, and claim 28 further requires that said microparticles are silica microparticles.

Pinkel teaches all the limitations of claims 18 and 26-27. Also, while Pinkel does not explicitly state that the microparticles are silica microparticles, Pinkel does separately teach microparticles and covalently attaching the target nucleic acids to silica (i.e. to form the binding agent). One of ordinary skill in the art would be motivated to use silica microparticles, because silica provides "a very low fluorescence substrate" and a "highly efficient hybridization environment" (column 9, lines 9-11), and the use of both microparticles and silica as the solid surfaces for the target nucleic acids provides a reasonable expectation that using silica microparticles would be successful. Therefore, it would have been prima facie obvious at the time the invention was made to use silica microparticles in a method of detecting aneuploidy, absent evidence to the contrary.

Response to arguments

Applicant's response traverses the rejection. However, the rejection is maintained for the reasons above. Applicant further argues that there is no reasonable expectation of success. However, it is unclear what applicant considers unreasonable, as methods of using a variety of types of particles, including silica microparticles, are well within the ordinary skill in the art for performing hybridizations, and this is further indicated by the reference teaching that the microparticles used can be silica microparticles. Therefore, applicant's arguments are not persuasive.

8. Claims 18-21, 23-24, 26-28 rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel as applied to claim 18 above, and further in view of Mohammed (Mohammed, US Patent Application Publication 2003/0124584, published

7/3/03). Claims 18 and 26-27 are described above. Claims 19-21 further require that said subject is a mammal selected from the group consisting of a human, a livestock animal, and an embryo. Claim 23 further requires that said embryo is generated using *in vitro* fertilization, and claim 24 further requires that said aneuploidy is detected in said embryo prior to implantation of said embryo.

Pinkel teaches all of the limitations of claim 18, as described above, however, Pinkel does not teach that the subject is a mammal selected from the group consisting of a human, a livestock animal, or an embryo; that said embryo is generated using *in vitro* fertilization; or that said aneuploidy is detected in said embryo prior to implantation of said embryo. Mohammed teaches a method of detecting aneuploidy, wherein said subject is mammal (page 2, paragraph 0015), said mammal is an embryo generated by *in vitro* fertilization (page 13, paragraph 0119), and said method results in preimplantation genetic diagnosis (i.e. detection of aneuploidy prior to implantation of said embryo) (page 13, paragraph 0119). One of ordinary skill in the art would be motivated to use an embryo generated by *in vitro* fertilization as the subject prior to implantation of said embryo, as means to select against abnormal embryos prior to embryo transfer (page 113, paragraph 0119). Since preimplantation genetic diagnosis using embryos is already performed in the art and since the use of microparticles as one means of detecting aneuploidy is already taught by Pinkel, substituting a microparticle-based method as method of detecting aneuploidy has a reasonable expectation of success. Therefore it would have been prima facie obvious at the time

the invention was made to use to use an embryo prior to implantation of said embryo as the subject in a method to detect aneuploidy, absent evidence to the contrary.

Mohammed also teaches a method of detecting genetic mosaicism (defined therein as "the presence of two or more chromosomally distinct cell lines" [page 13, paragraph 0118], i.e. detection of aneuploidy between cell lines) in livestock (page 13, paragraph 0120). One of ordinary skill in the art would be motivated to detect aneuploidy in livestock, because "screening founder animals for germline mosaicism prior to mating would reduce the costs associated with the propagation of transgenic lines" (page 13, paragraph 0120). Since testing for genetic mosaicism in livestock is already known in the art and since the use of microparticles as one means of detecting aneuploidy is already taught by Pinkel, substituting a microparticle-based method as a method of detecting aneuploidy/genetic mosaicism in livestock has a reasonable expectation of success. Therefore, it would have been prima facie obvious at the time the invention was made to detect aneuploidy in livestock, absent evidence to the contrary.

Response to arguments

Applicant's attention is drawn to the response to arguments presented in the 102 rejection above with regard to arguments against the Pinkel reference.

Applicant further argues that the ordinary artisan would have no expectation of success by combining Pinkel with Mohammed. This argument has been reviewed but is not persuasive because both methods involve determining changes in number of copies of target sequences in a sample. Therefore, the ordinary artisan would have a

reasonable expectation of success at the time of the invention for detecting copy number using the method of Pinkel in any biological samples including those described by Mohammed.

9. Claims 18-22, 23-24, 26-28, and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel and Mohammed as applied to claims 18-21, 23-24, and 26-28 above, and further in view of Ibanez (Ibanez E, et al. Assessment of the proportion of transgene-bearing sperm by fluorescence in situ hybridization: a novel approach for the detection of germline mosaicism in transgenic male founders. Mol Reprod Dev. 2001 Feb;58(2):166-72). Claims 18-21, 23-24, and 26-28 are described above, and claims 22 and 34 further require that said subject is a livestock animal selected from the group consisting of cattle, sheep, and horses.

Pinkel and Mohammed teach a method of detecting genetic mosaicism (i.e. aneuploidy) in livestock, as described above. Pinkel and Mohammed do not teach that the livestock animal is selected from the group consisting of cattle, sheep, and horses. However, Ibanez teaches a method of detecting genetic mosaicism (pages 167-168) that can be used for cattle and sheep (page 166, see introduction; page 171, see conclusion). Again, one of ordinary skill in the art would be motivated to detect aneuploidy in livestock, and specifically cattle and sheep, because "screening founder animals for germline mosaicism prior to mating would reduce the costs associated with the propagation of transgenic lines" (Mohammed, page 13, paragraph 0120). Since testing for genetic mosaicism in livestock is already known in the art and described in Mohammed and since the use of microparticles as one means of detecting aneuploidy

is already taught by Pinkel, substituting a microparticle-based method as a method of detecting aneuploidy/genetic mosaicism in cattle or sheep has a reasonable expectation of success. Also, Ibanez suggests that a method of detecting genetic mosaicism used for mice would also work in cattle or sheep, further supporting that a method of detecting aneuploidy in cattle and sheep would be successful. Therefore it would have been prima facie obvious as the time the invention was made to detect aneuploidy in sheep or cattle, absent evidence to the contrary.

Response to arguments

Applicant's attention is drawn to the response to arguments presented in the 102 rejection above with regard to arguments against the Pinkel reference.

Applicant further argues that the ordinary artisan would have no expectation of success by combining Pinkel with Mohammed and Ibanez. This argument has been reviewed but is not persuasive because it is unclear what is considered unreasonable. All of the methods involve determining changes in number of copies of target sequences in a sample. Therefore, the ordinary artisan at the time of the invention would have had a reasonable expectation of success in combining the method of Pinkel with any other biological sample, including those suggested by Mohammed and Ibanez.

10. Claims 18-21, 23-28 rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel and Mohammed as applied to claims 18-21, 23-24, and 26-28, and in light of Gvakharia (Gvakharia M, et. al. Single in vitro fertilization (IVF) cycle with blastomere biopsy for preimplantation genetic diagnosis (PGD) of Huntington's disease, assisted

hatching and cryopreservation results in healthy baby and subsequent ongoing pregnancy. Fertility and Sterility. 2002 Sept; 78(Supplement 1):S229).

Claims 18-21, 23-24, and 26-28 are described above, and claim 25 further requires that said sample originate from a blastomere.

Pinkel and Mohammed teach all the limitations of claims 18-21, 23-24, and 26-28, as described above.

While Mohammed teaches that the sample be an embryo, Mohammed does not specifically state that the sample originated from a blastomere. However, Mohammed does state that the method is used for preimplantation genetic diagnosis, and it is standard technique in the art to collect cells from the blastomere stage to perform preimplantation genetic diagnosis. See, for example, Gvakharia. Therefore, one of ordinary skill in the art would have been motivated to derive the sample from a blastomere and it would have been prima facie obvious at the time the invention was made to use cells from a blastomere in the method to detect aneuploidy as part of preimplantation genetic diagnosis. Since use of blastomeres is standard procedure for preimplantation genetic diagnosis, there is a reasonable expectation that use of blastomeres in any method for detecting aneuploidy would be successful, absent evidence to the contrary.

Response to arguments

Applicant's attention is drawn to the response to arguments presented in the 102 rejection above with regard to arguments against the Pinkel reference.

Applicant further argues that the ordinary artisan would have no expectation of success by combining Pinkel with Mohammed in light of Gvakharia. This argument has been reviewed but is not persuasive because it is unclear what is considered unreasonable. The methods of Pinkel and Mohammed both involve determining changes in number of copies of target sequences in a sample. Therefore, the ordinary artisan at the time of the invention would have had a reasonable expectation of success in combining the method of Pinkel with any other biological sample, including those taught by Mohammed. Also, Gvakharia is only supplied to demonstrate that Mohammed necessarily teaches using a blastomere by teaching the method for use in preimplantation genetic diagnosis. Therefore, Pinkel in view of Mohammed necessarily teaches all of the limitations of claim 25.

11. Claims 18, 26-29 rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel as applied to claims 18 and 26-28 above and in further view of Bitner (Bitner, et al. US Patent Number 6,787,307). Claims 18 and 26-28 are described above. Claim 28 further requires that said silica microparticles are silanized.

Pinkel teaches all the limitations of claims 18 and 26-28 as described above.

Pinkel does not teach that the silica microparticles are silanized. However, Bitner teaches a method of detecting nucleic acid sequences in a sample using silica microparticles that are silanized and coupled to nucleic acids. One of ordinary skill in the art would be motivated to use silanized silica microparticles in order to increase the binding of said polynucleotide to the microparticle. Also, because nucleic acid hybridization techniques and matrices have high fidelity under many circumstances,

there is a reasonable expectation that the silanized silica microparticles used in the method of Bitner would be successfully used as the silica microparticles in the method of Pinkel. Therefore, it would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to use silanized silica microparticles for the method of detecting aneuploidy of Pinkel, absent evidence to the contrary.

Response to arguments

Applicant's attention is drawn to the response to arguments presented in the 102 rejection above with regard to arguments against the Pinkel reference.

Applicant also argues that the ordinary artisan would have no expectation of success by combining Pinkel and Bitner. This argument has been reviewed but is not persuasive because it is unclear what is considered unreasonable. Silanized silica microparticles are commonly used in the art for nucleic acid hybridization methods. Therefore, the ordinary artisan at the time of the invention would have had a reasonable expectation of success in using the silanized silica microparticles of Bitner in the method of Pinkel.

Conclusion

12. None of the claims have been allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jaime M. Greene whose telephone number is 571-270-3052. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JMG 12/7/07

JEANINE A. GOLDBERG
PRIMARY EXAMINER
12/10/07